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Low grade serous tumours

Prof Sehouli: So, thank you very much for the possibility to discuss with you low grade ovarian cancer, and we know that we have more than one disease. We have several subtypes in ovarian cancer, and it started with the hypothesis to see that there's a high-grade pathway starting with a cyst, for instance, and then jump into high grade ovarian cancer, stage three, stage four. And then, we have a pathway where you'll see a cyst, a adenoma, a borderline and then a G1 cancer. So, it's a low-grade ovarian cancer pathway, and it's a step-by-step evolution, like we know this from colon cancer. And that's maybe the reason why we failed so far in introducing screening methods, because if you are able to catch a cancer, an ovarian cancer, then it is maybe the low grade, but never the high-grade ovarian cancer. And that's maybe one reason why we are not so far in early detection, early diagnosis. So, we know that ovarian cancer has several subtypes. They're even not homogeneous. And what you know is that we have the pre-malignant lesions in the fallopian, but that's only for patients who have a high-grade ovarian cancer. Low-grade ovarian cancer is located on the ovary, on the surface. And that's even the reason that to prevent ovarian cancer, it's only by using the prophylactic ovarectomy and salpingectomy, it's for the high-grade ovarian cancer who are, as you saw, it was BRCAness. That's, I think, really important if you try to preserve fertilities. So, for ovarian, to preserve them, but to preserve the fallopian makes only sense to prevent high-grade ovarian cancer. When we look back behind the histological subtype of serous, endometrial, clear cell cancer, mucinous cancer. Then, we see a different molecular tumor pattern, and we know that P53 is generally mutated in high-grade ovarian cancer, but not in low-grade. It's not exclusively, but in general, it's not mutated to P53. And we see in low-grade ovarian cancer, much high, prevalence of KRAS and NRAS, for instance, what we know for other tumor types, including colon cancer. So, you know that the classification for low-grade ovarian cancer was dramatically changed in 2014, because previously it was discriminated borderline tumors based on the diagnosis of the ovary, independent from the prevalence of implants out of the pelvis and formally, it was discriminated between invasive implants and non-invasive implants. And we know that if a patient has invasive implants, then, the overall survival dropped down significantly from close to hundred percent to 65%. In 2014, it was defined that if a patient has invasive implant, then, the diagnose from borderline tumors has to change to low-grade ovarian cancer. And that's very important even to know who are the patients who really have an in-favor prognosis and who not. But again, and I will have later finally a slide, that if you have a patient diagnosed before 2014, and it's stated in the document, that's a great too, that it's maybe a low-grade ovarian cancer, not a high-grade ovarian cancer. And the definition for low-grade and high-grade based only in

general, only, on Zeros cancers. So, if you have endometrial cancer, grade two, it's more likely that it is a low-grade than a higher grade and it's confusing, but it's wonderful because we understand more and more the really understanding of personalized diagnosis and personalized treatments. So, if you have a patient with a slow growth tumor, and this is a low-grade cancer, in general, they have even time to become big. And in general, the symptoms are low because these patients generally have no ascites and no pleural effusion. And even the biomarkers, I will just show this in the next slide, are slightly increased. And if you have a big tumor, it's always better as a surgeon because the tumor biology must be nice. Otherwise, it's impossible to become so big. And it's much more like in the triple negative breast cancer, small tumor ends high metastases. So, and you know, that fresh frozen is very limited to low-grade. So, every tumor, is highly proliferated, highly differentiated, the diagnosis is very difficult to make. And that's reason I always recommend to make a two-stage approach. If you have a tumor where you are not sure because treatment is different; in high-grades, in generally you need much more lymph node dissection if the lymph node is not microscopically suspicious. And in borderline tumors, you know, it's contraindicated to do a lymph node dissection, even in early stage. And that's, I think, the reason why we know, especially, in mucinous cancer, that's predictive value of a fresh frozen depends on the resources we have, but it's around 70%. Sometimes, you can even go in a coin because you don't need only the phenotype in the microscopic picture, you need even immunohistochemistry and maybe even molecular pathology to make the final diagnosis. And what is really important is that if you have an implant and metastasis in the peritoneum cavity then, you can have different stages on the evolution. So, you can have non-invasive implant, beside invasive implant. If you see by laparoscopy or by open surgery, the patient has hundreds of lesions. You cannot be sure that all hundred lesions are non-invasive. So, if you take 1, 2, 5, 10, 20 lesions, you cannot translate this to the majority. And this is a case I did surgery on a post-menopausal woman, and I did I think four or five fresh frozen, but I nevertheless, I resected the lesion. And at the end of the day, there was one or two lesions who are in the stage of low-grade cancer. So, this is the recommendation, complete resection must always be the key- procedure in the management of low-grade ovarian cancer. So, I tried to summarize even the different tumor types in ovarian cancer. You have patients who are symptomatic and asymptomatic, low-grade cancer patients have, in general, not the problem of a compartment because, in general, they have very few ascites, few symptoms based on the low proliferation, the low Ki-67. And then you have patients who are peritoneal and lymph nodes dominated; in low-grade ovarian cancer you have many patients with lymph node metastases. And you know, if you have a lymph node metastasis without pattern [Audio Not Clear] even the prognoses in general are better because it's not a life-threatening problematic, such as bowel obstruction or the secondary effects of ascites or sarcopenia with pneumonia, all the others indirect collateral signals. So, the CA125, is not bad at all. I like it. I like biomarker, but you have to know that we cut off what we have in the lab for high-grade ovarian cancer, different in low-grade. And it's different if you have endometrial cancer or mucinous; CA125 is only in general, for CA125 sensitive tumors, affecting the peritoneal cavity with a high- proliferation rates, but you know, in fyb rate in adenomyosis and endometriosis you can even have high CA125. So, look on the individual cutoff and then look how is the dynamic, from 10 to 20, 20 to 30, It's a different story, but it's additionally. So, but you know, that CA125 and even HG4 is not so high and you cannot believe it. I do it because better than nothing, but be careful because especially in very low perforated tumors it's dynamic, because it's even the response of your immune system and your inflammation process that CA125 cannot be very high. So, but in general, it's significant, lower than in high-grade. Lymph node dissection. You know, it's a complex story. LION is for advanced diseases with peritoneal-affected disease without any suspicious lymph node. Then, it makes no sense for survival, and even for progression-free survival to resect lymph nodes. It's a different story if you have affected lymph nodes, and it's a different story in early stage and we did a publication in lymph node dissection early-stage ovarian cancer, and, yes, we see even higher rates in the pelvic region then in high-grade ovarian cancer, maybe based on endometrial clear cell and all the other stories. So, the chemotherapy in borderline and low-grade is very heterogeneous because the discrimination between high and low-grade is something new. And the studies looking on this issue are generally much older before we changed the classification. So, and there wasn't in generally a no second pathology and all limitations, but

we have seen that the impact of patient even with implants was limited. And you know, that we know a little bit about high-grade cancer with introducing bevacizumab has entered genius drug as a first maintenance approach in the three-column model. And we know that low-grade ovarian cancer even retrospectively without reference pathology, the effect was not so strong. Despite the fact that only a few patients were been enrolled. The label for Bev is independent from low and high-grade because the introduction of Bev was before 2014. Nevertheless, there are some data showing some efficacy using Bev. So, that's the reason in advanced diseases we like to offer this and I'm trying my best that we have further data if to see if really Bev is helping the patients; at the moment, we'll say, give it, but the data are not really robust in advanced low-grade ovarian cancer. So, the knowledge about borderline low-grade cancer is really still limited. And that's the reason why we have to train all the physicians, but even to educate patients, the most robust data we have, it's from the ROBOT-STUDY, it's a German study with all our centers and we looked how many patients, borderline tumor, are misdiagnosed. You see even centers who believe they are good, they have in the second, in the reference pathology, up to 11% that this diagnosis was not confirmed. And even from these 92 patients, 40 has a cancer. And 52 have nothing, not a cancer, and dramatically because you know, what are the consequence, surgery, chemotherapy and all those stories. So that's the reason why we strongly recommend in borderline tumors in solid tumors to make a reference pathology and even to use molecular pathology as a backbone. So, what we have seen in this study, what is published already, that patients who underwent incomplete surgery and that requirements are very low, have a significant different progression-free survival because you underestimate the real cancers. And that's really important that you have adequate staging of these patients. What not means always laparotomy, but you have to know, are there any lesions? If you see a lesion, we do always open surgery because you cannot identify all lesions by laparoscopy, whatever you believe and want to see. So, if we see from the one thousand patients from ROBOT you see that 74 patients relapsed. And from the 74, half of them have, again, a borderline tumor without cancer lesions and the other 22 patients have invasive cancer. And you'll see that 36 will have a high-grade. So, there are some patients have borderline, again, the other half will have cancerous, two-third will have low-grade, and one third will have high-grade. It's not clear if it's really possible that from low-grade to high-grade can change, but it's very cellular because in general, low-grade is always low-grade. The stage can be different, but the histology should be a high differentiated disease. So, you see, if you clean low-grade from borderline, you see that borderline in general have a hundred percent overall survival. And that is the difference. So, staging and diagnosis is the crucial aspect. So, if we look on the chemotherapy for low-grade is very complex because if you look on the response rate on the PFS value, you will be depressed. And Jacek Grabowski is one of my consultants that meta-analyzes and what we have seen that low-grade ovarian cancer always has a better outcome. And, but the response rate, again, is limited. Nevertheless, the survival is better. So, the question is its response, read the target in low-grade cancer. If you have a tumor with a low proliferation rate, how it can it have shrunk? Or if the effect of chemotherapy on the environment, or do we have other alternatives to preserve chemotherapy? That's open questions. So, and if you look on these, you see even the impact of surgery because surgery is the backbone for high-grade but even in low-grade ovarian cancer, and you see that even the tumor debulking makes sense. And that's the reason why we strongly recommend to go to surgery and to do your best even to reduce up to 10-centimeter because every tumor reduction, and that's different to high-grade, makes impact because you have even not so much adjuvant or sequential regimens using medical treatments. And you see the low-grades have the best prognosis than the high-grade completely resected. And if you have residuals, you see the low-grade, less than one centimeter is close to the patient who is high grade without residuals, that's for the PFS and for the high-grades, it is the same story. Yes. That you'll see that the low-grade reduction lesser centimeters running closer to the complete resection of high-grade; that's I think very important for surgery and to ask for low-grade ovarian cancer, what maintenance approach we can offer based on the three- column model for high-grade ovarian cancer. I already mentioned the bevacizumab story and there's one study, it's a retrospective study, it's not prospectively, from the MD Anderson. They have one arm, was observation, and then the other was a sequential, anti-hormonal treatment, mostly, letrozole after chemotherapy response, and the decision who

require nothing of those was based on feelings from the doctors, there was no algorithm and no protocol forces. Nevertheless, the impact was significant for progression-free survival. You'll see a benefit for patients who received the combination of chemotherapy and sequentially the anti-hormonal treatment. And this is the reason why we offer this in patients with advanced cancers to add that, we have no data at the moment to combine Bev plus Letrozole. But I think we need to explore this because these patients have a high need for better treatments. So, the Ki-67 is generally high in high-grades and then low-grade ovarian cancer, we love if the median between five to seven, but we have seen this strong association between Ki-67 and response of chemo, and even as a prognostic marker. So, this is really important, and to bring this as an idea to stratify patients, even for chemo and non-chemotherapy strategies. So that's, I think important why we always demand to measure Ki-67 in the tumor tissue of these patients, because this was associated with response and prognosis. So, if we have relapse of low-grade ovarian cancer, it's difficult because the older discrimination between PARP resistance platinum sensitivity is not clear for people low-grade because they are all of them sensitive at all. But what you mean is the time-periods and you know, we levered it even for the high-grade. We don't want to use this term, platinum-resistant, and even not to use the six- or three-months interval because it's only emotional and even based on what, on the availability of MRI or whatever. So, we look always, if the reference pathway is available, second, we always make a reliable analysis. If the diagnosis is older than 2014, we look for studies. We have one study now with checkpoint inhibition, and we have one study that opened now with trabectedin and doxorubicin. And we look on the molecular pattern, PARP inhibition, we have up to 5, sometimes 10% HRD positivity. There's no data for PARP as a mental approach in low-grade. And generally, they are BRCA negative, but this can be an option if you'll have the signal, we offer at the moment Bev, anti-hormone treatment. Yes, don't use Tamoxifen. I talk with Dr Gachon. So, most activities came from the aromatase inhibitors and trametinib is an option. I will show you this in relapse ovarian cancer and the chemotherapy we did a meta-analysis in my department and at the local society. And we already address it. Platinum-sensitive is not a marker for a low-grade ovarian cancer and is independent. So, about trametinib and other chemotherapy. I want to highlight this study from Ignace Vergote where the MEK inhibitor but the study was in general a negative study. Despite the fact there is some impact on PFS, but it was not strong enough in comparison to classical chemotherapy. The trametinib is an option that I really like, toxicity is good, just a little bit skin toxicity, but based on this study from the colleagues from the National Cancer Research Institute, it was superior to the control arm with chemotherapy or aromatase inhibitors. And that's the reason that I frequently apply for the patients this treatment option. So, this is the key, it's... I already mentioned that the PARP inhibition that we introduced was niraparib, and even with olaparib based on PRIMA and PARP is not actually an option for low-grade ovarian cancer. The different treatment options are summarized on this table. And it's really, really important that we increase our research activities and not to exclude these patients from our current trials. And I want to highlight Dr Virchow who was a pathologist, but he was even a researcher. He was also an anthropologist and a humanist and a politician. And I think it's really important for doctors who are dedicated to women cancer to see always the holistic approach and to see the whole story of the individual patients. Thank you very much for your attention.